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Clinical Trial

Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: Results from a British Thoracic Oncology Group randomised phase III trial

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Quality of life

Abstract ***Background:*** Platinum-based combination chemotherapy is standard treatment for the majority of patients with advanced non-small-cell lung cancer (NSCLC). The trial investigates the importance of the choice of platinum agent and dose of cisplatin in relation to patient outcomes.

Methods: The three-arm randomised phase III trial assigned patients with chemo-naïve stage IIIB/IV NSCLC in a 1:1:1 ratio to receive gemcitabine 1250 mg/m^2 on days 1 and 8 of a 3-week cycle with cisplatin 80 mg/m^2 (GC80) or cisplatin 50 mg/m^2 (GC50) or carboplatin AUC6 (GCb6) for a maximum of four cycles. Primary outcome measure was survival time, aiming to test for a difference between treatment arms and also assess non-inferiority with pre-defined margin selected as hazard ratio (HR) of 1.2. Secondary outcome measures included response rate, adverse events and quality of life (QoL).

Findings: The trial recruited 1363 patients. Survival time differed significantly across the three treatment arms ($p = 0.046$) with GC50 worst with median 8.2 months compared to 9.5 for GC80 and 10.0 for GCb6. HRs (adjusted) for GC50 compared to GC80 was 1.13 (95% confidence interval [CI] 0.99–1.29) and for GC50 compared to GCb6 was 1.23 (95% CI: 1.08–1.41). GCb6 was significantly non-inferior to GC80 (HR = 0.93, upper limit of one-sided 95% CI 1.04). Adjusting for QoL did not change the findings. Best objective response rates were 29% (GC80), 20% (GC50) and 27% (GCb6), $p < 0.007$. There were more dose reductions and treatment delays in the GCb6 arm and more adverse events (60% with at least one grade 3–4 compared to 43% GC80 and 30% GC50).

Interpretation: In combination with gemcitabine, carboplatin at AUC6 is not inferior to cisplatin at 80 mg/m^2 in terms of survival. Carboplatin was associated with more adverse events and not with better quality of life. Cisplatin at the lower dose of 50 mg/m^2 has worse survival which is not compensated by better quality of life.

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1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1] and is responsible for more than 20% of cancer deaths in the United Kingdom [2]. Non-small-cell lung cancer (NSCLC) accounts for more than 80% of lung cancers and poor outcomes are driven by the fact that the vast majority present at clinic with advanced disease [3]. This paper reports a large randomised phase III trial in advanced NSCLC, set up by the British Thoracic Oncology Group (the BTOG2 trial), to provide definitive evidence to inform choice of standard first-line treatments. Early presentations of the results from the trial have already influenced clinical practice and this paper provides the final conclusive published evidence.

There is continued uncertainty about the optimal first-line chemotherapy for patients with advanced NSCLC and hence clinical practice remains variable. Platinum-based combination chemotherapy was firmly established following a meta-analysis of eight cisplatin randomised trials [4] which was later confirmed by an updated meta-analysis of 16 further trials [5] but there was ongoing ambiguity about whether cisplatin or carboplatin gave better patient outcomes. This was driven by conflicting trial results, in particular emerging results from an influential UK trial giving evidence that carboplatin with gemcitabine gave better survival than cisplatin (low dose 50 mg/m^2) combined with mitomycin and ifosfamide [6] and a meta-analysis of five trials suggesting that in combination with third generation drugs, such as gemcitabine and taxanes, cisplatin gave better survival and higher radiological response rates than carboplatin [7].

In addition, there was uncertainty about the preferred dose of cisplatin due to a lack of definitive evidence, with practitioners in the UK more inclined to opt for the lower dose of 50 mg/m^2 every three weeks [6] than counterparts in Europe and the United States which considered 75–100 mg/m^2 as standard [8,9]. The cisplatin burden of intravenous hydration and inpatient administration together with the toxicity of emesis, neuropathy and perception of poor tolerance led many clinicians to adopt carboplatin as the preferred option. Carboplatin however is largely renally cleared and must be correctly dosed according to glomerular filtration rate (GFR) [10] and measurement of GFR with 51-Cr-EDTA is cumbersome and expensive. Even when dosed optimally, carboplatin causes more severe neutropenia and thrombocytopaenia than cisplatin [11]. The BTOG2 trial aimed to resolve this cisplatin versus carboplatin debate.